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The Effects of Extracellular Protons on the hERG Potassium Channel

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The α -subunit of channels mediating the cardiac rapid delayed rectifier current (I_{Kr}) is encoded by the *human Ether-à-go-go-Related Gene (hERG)*. Macroscopic hERG current (I_{hERG}) amplitude is reduced and deactivation kinetics are accelerated with extracellular acidosis. We have investigated the single channel basis for the effects of acidic external pH (pH_e) on the isoforms of I_{hERG} expressed in myocytes (hERG1a and 1b). Patch clamp recordings were made at room temperature with the extracellular superfusate (whole-cell) or pipette solution (cell attached) acidified to pH 6.3 compared with control (pH 7.4). A decrease in pH_e to 6.3 caused acceleration in deactivation and a reduction in maximal whole-cell conductance of $\sim 34\%$ for I_{hERG1a} ($n=8$ cells) and of $\sim 36\%$ for I_{hERG1b} ($n=5$ cells). Single channel recordings were made with isotonic potassium (140 mM) bathing the cells and in the electrode. Channel amplitude and open state kinetics were measured at a series of repolarisation voltages following a depolarising command to +40mV. Slope conductance values derived from amplitude current-voltage relationships between -120 and -40 mV were 12.3 ± 0.2 pS for pH 7.4 ($n=10$ cells) and 9.3 ± 0.1 pS for pH 6.3 ($n=9$ cells) ($P < 0.01$, two-tailed t-test) for hERG1a. The corresponding values for hERG1b were 11.4 ± 0.2 pS for pH 7.4 ($n=6$ cells) and 7.6 ± 0.4 pS for pH 6.3 ($n=5$ cells) ($P < 0.0001$; two-tailed t-test). Open-time kinetics at -120 mV for hERG1a were reduced from 8.49 ± 1.0 ms in control ($n=8$ cells) to 4.2 ± 0.4 ms in pH_e 6.3 ($n=7$ cells) ($P < 0.05$; two-tailed t-test). The hERG1b open state kinetics were 5.7 ± 0.6 ms in pH_e 7.4 ($n=6$ cells) and reduced to 3.1 ± 0.7 ms in pH_e 6.3 ($n=5$ cells) ($P < 0.05$; two-tailed t-test). Thus, it can be concluded that a reduction in the single channel conductance and acceleration of open-times contribute to the attenuation of macroscopic I_{hERG} when exposed to acidic pH_e .